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PITT-ROGERS-DANKS SYNDROME: THE RESULT OF A 4p MICRODELETION

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Pitt-Rogers-Danks syndrome (PRDS) is a rare, presumed autosomal recessive, syndrome with pre- and postnatal growth retardation, microcephaly, characteristic facial appearance, seizures, unusual palmar creases and developmental delay. Since the first description in 1984, only 7 cases have been reported. We report the identification of a 4p microdeletion in 2 new patients, who were previously diagnosed with PRDS, as well as the sibs in Pitt et al. [1984]. PRDS can no longer be considered autosomal recessive. Although our cases are attributable to a microdeletion in 4p16, it is uncertain if the critical region involves a single locus or multiple loci or to what extent this region overlaps with the critical region for Wolf-Hirschhorn syndrome.

KEY WORDS: Pitt-Rogers-Danks syndrome, Wolf-Hirschhorn syndrome, 4p microdeletion, fluorescence *in situ* hybridization

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INTRODUCTION

The Pitt-Rogers-Danks syndrome (PRDS) has been described as a rare condition consisting of pre- and postnatal growth retardation, microcephaly, characteristic facial appearance, seizures, unusual palmar creases and developmental delay. The typical facial traits include wide mouth, short upper lip with flat philtrum, beaked nose, prominent eyes, telecanthus, slanted palpebral fissures and maxillary hypoplasia. This syndrome was first described in 1984 [Pitt et al.,1984]. Since then, only 7 cases have been reported [Pitt et.al., 1984; Donnai, 1986; Oorthuys and Bleeker-Wagemakers, 1989; Lizcano et al., 1995]. Autosomal recessive inheritance has been presumed (OMIM #262350) because the original paper by Pitt et al. described 2 affected sisters born to clinically normal parents. Although clinical similarity to Wolf-Hirschhorn syndrome (WHS) has been noted, all reported PRDS patients have had apparently normal karyotypes.

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WHS is associated with a deletion of the short arm of chromosome 4. This deletion can be the result of a terminal or interstitial deletion or a translocation. The deletions vary in size, and the clinical severity does not correlate with the size of the deletion. The critical region for WHS has been placed in distal 4p16.3. A more proximal interstitial deletion of 4p14-16 causes a different, clinically recognizable syndrome [White et al., 1995].

With the introduction of a commercially available DNA probe for WHS, we elected to perform fluorescence *in situ* hybridization (FISH) analysis for WHS on our patients who had been diagnosed with PRDS. We report a 4p microdeletion in 2 new patients and the 2 sisters of Pitt et al. [1984].

CASE REPORTS

Patient 1

This female patient was born to a 24-year-old gravida II, para I mother after an uneventful pregnancy. By dates and the mother's estimation she was 41 weeks, but based on ultrasound study performed at the end of the second trimester she was only 38 weeks. Birth weight was 2300 g (<10th centile for 41 wks) and birth length 48 cm (10th centile for 41 wks). Neonatally she was hypotonic and required several extra days in the hospital because of inadequate temperature control. She experienced a grand mal seizure at age six months and has since had a seizure disorder. She has had slow growth. At age six years her weight was 13.1 kg, length 100 cm and OFC 42 cm. All of these measurements are far below the 5th centile.

Her facial appearance was quite distinctive due to her short lower facial height, wide mouth, short philtrum, maxillary hypoplasia, vertically short mandible and slightly beaked nose (Fig. 1). Her ears are simple, slightly low-set, and somewhat anteverted. Her eyes are prominent, giving her a wide-eyed appearance but lacking true hypertelorism. Her neck, chest, abdomen and back are thin, but otherwise unremarkable. Her limbs are normally proportioned and she is mildly hyperextensible. She has bridged palmar flexion creases with extra palmar creases, bilaterally. She is hypotonic, but has no localized neurologic abnormalities. Her mental development has been slow. She walked at 28 months and began to babble at age 4 to 5 years.

Previous evaluations had not resulted in a definitive diagnosis. We initially made the diagnosis of PRDS. The parents sought a second opinion regarding this diagnosis and sent her photographs and medical summary to another one of the present authors (J.G.R.), who confirmed the diagnosis of PRDS. Since some of the phenotypic findings of PRDS overlap with WHS, FISH using the D4S96 chromosome 4p16.3-specific probe (Wolf-Hirschhorn region Oncor, Inc.) was performed. Twenty metaphase cells were analyzed with FISH. All of the cells contained a deletion of the 4p16.3 region on one of the number 4 chromosomes. Chromosome and FISH studies on her parents were normal.

Figure 1. Patient 1 at 7 9/12 years of age. Note the wide mouth and flat nasal bridge and glabella.

Patient 2

This female patient was the product of a full term pregnancy to a 28-year-old gravida II, para I mother who had been treated with Clomid®. Although known to be at 40 weeks of gestation she was judged to be 36 weeks by exam. She had respiratory distress syndrome, mild nonpathological jaundice, and peripheral pulmonary hypertension secondary to anemia for which she was transfused. Patent ductus arteriosus resolved spontaneously. Birth weight was 2100 g (<10th centile), length 56 cm (>90th centile) and OFC 31 cm (<10th centile). She has had

continued slow growth, and at 11 years weight and head circumference are below the 5th centile (Fig. 2).

Her skull shape is normal with prominent forehead and proptotic eyes due to hypoplastic orbits. She has a very hypoplastic maxilla with a narrow arched palate, and micrognathia with a relatively open mandibular angle. Ears are relatively large compared to other facial parameters, with hypoplastic lobules and open helices. Neck and chest are normal but thin. She has a short sternum, and limbs are long and lean with hyperextensible joints. Palmar and digital flexion creases are normal with an extra flexion crease on the thumb. She walked at 3 1/12 years, began using single words at 2 years but was not able to put a full sentence together until age 5 years. She is mainstreamed in school with relatively normal social skills but delayed academic skills. She is treated with Clonidine® for attention deficit. She experiences seizures with fever and has been tried on phenobarbital and Dilantin®, but has had allergic reactions to both of these medications.

The diagnosis of WHS was considered ; however, chromosome studies were performed at other laboratories on two occasions and were reported as normal. The diagnosis of PRDS was made and confirmed by Dr. John M. Opitz.

We obtained a peripheral blood specimen and performed chromosome analysis and FISH studies. High resolution chromosome banding (725 band level resolution) suggested a deletion of the terminal p arms of one chromosome 4 (46,XX,del(4)(p16.3). FISH using the probe D4S96 from the WHS critical region was performed to confirm the cytogenetic results. Twenty metaphase cells were analyzed with FISH and all cells were found to be deleted in one of the number 4 chromosomes.

Pitt et al., [1984] A & B

The original paper of Pitt et al. [1984] described these sisters, now young adults, with PRDS born to clinically normal parents. We obtained prepared slides from these sibs and performed FISH using the D4S96 chromosome 4p16.3-specific probe which identified a deletion of the 4p16.3 region on one of the number 4 chromosomes in both women. Subsequently, we obtained prepared slides from their parents. Using the same FISH probes, their mother had a normal karyotype and their father was identified as having a balanced translocation (46,XY,t(4;8) (p16.3;p23.1). Thus, the karyotypes of the 2 affected women can be reinterpreted as 46,XX, -4 +der 4 t(4;8)(p16.3;p23.1) pat.

DISCUSSION

Based on the observation of deletion 4p16.3 in 4 PRDS patients including the only known pair of affected sibs, PRDS can no longer be considered an

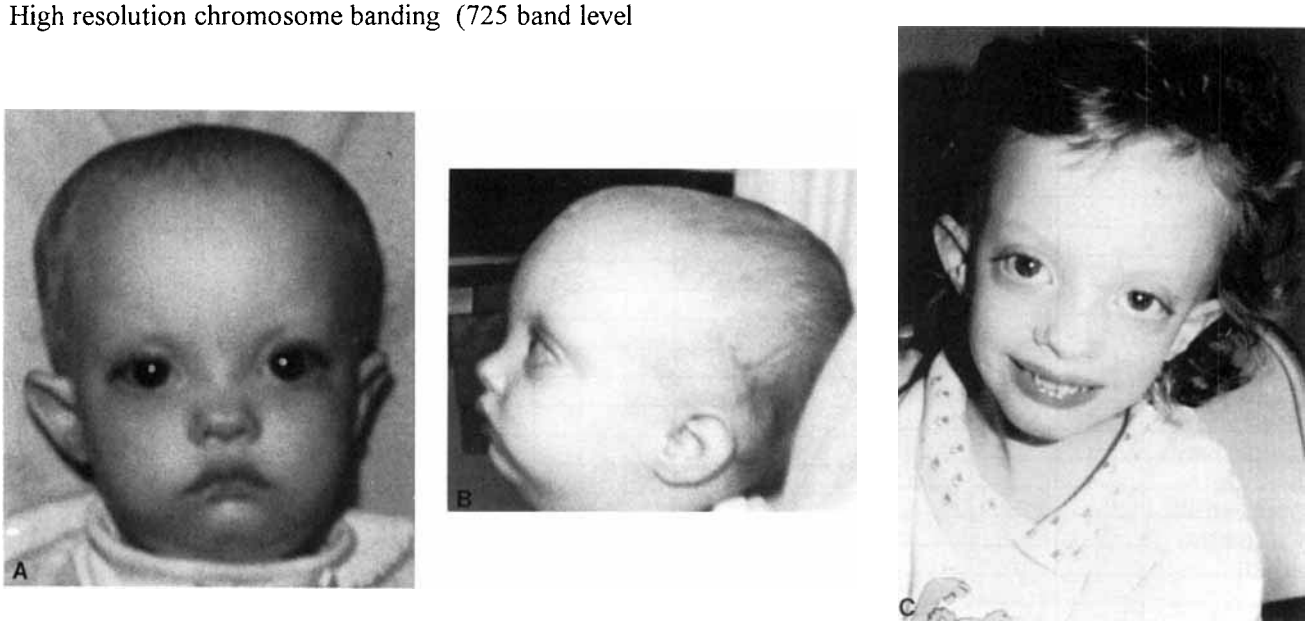

Figure 2. A. Patient 2 full face at 5 months of age. Note resemblance to patient 1. B. Patient 2 profile at 5 months of age. C. Patient 2 at 4 8/12 years of age. Her facial appearance is suggestive of WHS.

autosomal recessive condition. Clearly the PRDS phenotype results from a microdeletion of 4p although it is not yet certain whether the critical region for PRDS is exactly the same as that for WHS. Clinically, PRDS and WHS have overlapping phenotypes, although the PRDS patients tend to be somewhat less severely affected with no reported infant or childhood deaths, fewer internal malformations, less severe developmental delay and less of the classical "Greek warrior helmet" facial appearance. All PRDS patients were at least 2 years old when reported and were free of life-threatening anomalies, while about one third of WHS patients die during the first 2 years. Only one of 9 PRDS patients had a congenital heart defect compared to about 50% of WHS patients (Table I). All PRDS patients either were ambulatory when reported or could be expected to become ambulatory, but most WHS patients do not learn to walk. Although PRDS and WHS share several facial characteristics such as high forehead, hypertelorism/telecanthus, beaked nose and short philtrum, some differences have been noted. The glabella is often flat in patients diagnosed with PRDS, but is usually prominent in WHS. None of the PRDS patients has cleft lip or palate while 40% of WHS patients have these anomalies. The wide mouth, which is characteristic of PRDS patients, was not mentioned in reports of WHS. Nevertheless there is significant clinical overlap. Some WHS microdeletion patients, such as the one described by Altherr et al.[1991], are only mildly to moderately developmentally delayed and show facial characteristics including flat glabella and wide mouth, which are more suggestive of PRDS. Patient 2, previously diagnosed with PRDS, is developing a "Greek warrior helmet" facial appearance consistent with WHS.

Several explanations for the observation of similar 4p16.3 microdeletions in PRDS and WHS are possible. PRDS may not be a separate clinical entity, but may be a mild form of WHS associated with the same microdeletion of 4p16.3 that has been recognized in classical WHS. Alternatively, PRDS may be a microdeletion syndrome with a slightly different critical region than WHS, and the clinical overlap may be due to most patients having a

TABLE I. Clinical Findings in Pitt-Rogers-Danks and Wolf-Hirschhorn Syndromes

	Pitt et al [1984]				Donnai	Oorthuys	Lizcano	Patient	Patient	WHS
	A	B	C	D	[1986]	[1989]	[1995]	1	2	
Growth										
IUGR	+	+	+	+	+	+	+	+	+	≈100%
Microcephaly	+	+	+	+	+	+	+	+	+	≈100%
Short stature	+	+	+	+	+	+	+	+	+	≈100%
CNS										
Dev delay	+	+	++	++	++	++	++	++	++	+++
Hyperactivity	+	+	+	+	?	?	?	+	+	common
Epilepsy	+	+	+	+	–	–	–	+	+	≈50%
Craniofacial										
High forehead	+	+	+	+	+	+	?	+	+	≈100%
Prom glabella	–	–	–	–	–	–	–	–	–	≈100%
Iris anomaly	–	–	–	–	–	+	–	–	–	≈35%
Hypertel/teleca	+	+	+	+	–	+	+		+	≈100%
Beaked nose	+	–	+	?	+	+	+	+	+	≈100%
Max hypoplasia	+	+	+	+	+	+	+	+	+	?
Short philtrum	+	+	+	+	+	+	+	+	+	≈100%
Cleft palate	–	–	–	–	–	–	–	–	–	≈ 40%
Wide mouth	+	+	+	+	+	+	+	+	+	–
Ear anomalies	?	?	+	+	?	+	+	+	+	common
Other										
Hyperextensibl	+	+	+	+	+	+	?	+	+	common
Extra creases	+	+	+	+	+	+	+	+	+	common
Clubfoot	–	+	–	–	–	+	–	–	–	common
Heart	–	–	–	–	–	ASD	–	–	–	≈50%
Sex	F	F	F	M	F	F	M	F	F	2F:1M

deletion that encompasses both critical regions. Detailed deletion mapping of the 4p16 region suggests that the typical facial phenotype of WHS is associated with deletions in the currently proposed critical region, while the growth retardation, hypotonia and developmental delay are not localized [Estabrooks et al., 1995]. Recently, the WHS critical region has been narrowed to approximately 1 Mb which ends just proximal to the commercially available probe D4S96 [Wright et al, 1995]. At least one patient with clinical WHS lacks any detectable deletion using the D4S96 probe, while a patient with ring 4 who is deleted for the probe has a phenotype that is not typical for either WHS or PRDS [Somer et al., 1995]. Although all the PRDS patients studied by FISH have a deletion for probe D4S96, the possibility that the syndrome results from nonfunction of a single gene in the deleted area cannot be excluded. If this hypothesis is correct, PRDS patients without a detectable deletion would eventually be found, and would not differ clinically from those with a microdeletion. Patients without a microdeletion born to normal parents would be presumed to have a new mutation which could potentially be transmitted to their offspring.

An imprinting or parent-of-origin difference, such as that distinguishing Prader-Willi and Angelman syndromes, can probably be ruled out. Imprinting as an explanation for the difference between WHS and PRDS seems unlikely, since both maternal and paternal origin of WHS have been described with no major clinical differences [Dallapiccola et al., 1993]. Parent-of-origin data is unavailable in PRDS, except for the 2 affected sisters who have deletion of the paternal chromosome 4, similar to that observed in most of WHS patients. Thus, there is no evidence that imprinting plays an important role in either WHS or PRDS.

In summary, 4 patients with PRDS, including the only known pair of affected sibs, were found to have microdeletions of 4p16.3 detectable with the probe D4S96. This probe is also used clinically for the diagnosis of WHS, although there is some evidence it may lie just outside the WHS critical region. The finding of similar deletions in these clinically overlapping syndromes could indicate either that PRDS is a mild form of WHS or that PRDS and WHS are due to deletion (or possibly mutation) of adjacent critical areas (or loci) near 4p16.3. In the latter case, the clinical overlap would be due to deletions encompassing both critical areas in many patients. Regardless of which of the above explanations ultimately proves correct, PRDS should now be considered a microdeletion syndrome. All patients with suspected PRDS should be karyotyped with FISH analysis using the D4S96 probe. The parents of any PRDS patient should also be karyotyped with FISH analysis to rule out translocations involving 4p16.3 before recurrence risk information can be provided. Cases due to unbalanced segregation of a parental translocation will present a significant risk of recurrence in sibs, while those due to *de novo* microdeletion will have only a low sib recurrence risk due to the possibility of gonadal mosaicism. No patient with PRDS has been known to reproduce, but vertical transmission as in other microdeletion or autosomal dominant conditions is predicted. Further analysis of the 4p16.3 region in PRDS and WHS patients will help to define the critical regions for both conditions.

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REFERENCES

Altherr MR, Bengtsson U, Elder FFB, Ledbetter DH, Wasmuth JJ, McDonald ME, Gusella JF, Greenberg F (1991): Molecular confirmation of Wolf-Hirschhorn syndrome with a subtle translocation of chromosome 4. Am J Hum Genet 49:1235-1242.

Dallapiccola B, Mandich P, Bellone E, Selicorni A, Mokin V, Ajmar F, Novelli G (1993): Parental origin of chromosome 4p deletion in Wolf-Hirschhorn syndrome. Am J Med Genet 47:921- 924.

Donnai D (1986): Brief clinical report: A further patient with the Pitt-Rogers-Danks syndrome of mental retardation, unusual face and intrauterine growth retardation. Am J Med Genet 24:29-32.

Estabrooks LL, Rao KW, Driscoll DA, Crandall BF, Dean CS, Ikonen E, Korf B, Aylsworth AS (1995): Preliminary phenotypic map of chromosome 4p16 based on 4p deletions. Am J Med Genet 57:581-586.

Lizcano LA, Garcia-Cruz D, Garcia-Cruz O, Sanchez-Corona J (1995): Pitt-Rogers-Danks

syndrome: Further delineation. Am J Med Genet 55:420-422.

Oorthuys JWE, Bleeker-Wagemakers EM (1989): A girl with the Pitt-Rogers-Danks syndrome. Am J Med Genet 32:140-141.

Pitt DB, Rogers JG, Danks DM (1984): Mental retardation, unusual face and intrauterine growth retardation: A new recessive syndrome? Am J Med Genet 19:307-313.

Somer M, Peippo M, Keinanen M (1995): Controversial findings in two patients with commercially available probe 4DS96 for the Wolf-Hirschhorn syndrome. Am J Hum Genet 57(supp):A127.

White DM, Pillers DM, Reiss JA, Brown MG, Magenis RE (1995): Interstitial deletions of the short arm of chromosome 4 in patients with a similar combination of multiple minor anomalies and mental retardation. Am J Med Genet 57:588-597.

Wright TJ, Denison K, Altherr MR (1995): Redefinition and molecular analysis of the critical region for the Wolf-Hirschhorn syndrome locus. Am J Hum Genet 57(supp): A233.